

Editorial

Delayed gastric emptying and prokinetic agents in continuous ambulatory peritoneal dialysis

Since its introduction by Popovich and Moncrief (1) more than 2 decades ago, continuous ambulatory peritoneal dialysis (CAPD) has remained the most common form of first-line dialytic therapy in Hong Kong (2). Despite its popularity, combating nutritional problems is still a challenge to the practicing nephrologist (3). Patients are often prescribed a high-protein diet to achieve nitrogen balance. Many patients, however, experience anorexia; and nausea and vomiting after food intake is frequently reported in the clinic. Over time, these patients lapse into a state of malnutrition, which is negatively correlated with survival (4).

An important cause of anorexic symptoms in CAPD is delayed gastric emptying, which could be the combined result of increased intraperitoneal pressure consequent upon the instillation of dialysis fluid, and autonomic gastropathy secondary to the underlying uremic and/or diabetic state. Previous studies using radionuclide techniques that measured the gastric transit time after the ingestion of a 99m technetium-labeled standard meal demonstrated prolonged gastric emptying in CAPD patients compared with normal controls, and gastroparesis is more pronounced among uremic diabetics (5).

To mitigate the clinical impact of gastroparesis, gastrointestinal promotility agents are often prescribed to CAPD patients. Cisapride, a serotonin receptor agonist with potent prokinetic properties originally designed for severe gastroesophageal reflux disease, is one of the most frequently used agents among CAPD patients in the past decade. The clinical efficacy of cisapride has been documented in one study, which reported increased plasma albumin levels after treatment in persistently hypoalbuminemic chronic dialysis patients who had poor gastric emptying (6).

In 1995, 2 years after its approval by the US Food and Drug Administration (FDA), there were "black box" warnings that cisapride (Propulsid®) could cause life-threatening cardiac arrhythmias, notably torsades de pointes, in patients susceptible either because of concurrent medications that interfere with cisapride metabolism or prolong the QT interval or because of other diseases that predispose to such arrhythmias. These warnings, together with subsequent health alerts issued

by the manufacturer, led to regulatory action in 1998 by the FDA that contraindicated the use of cisapride in such patients (7). Further data from the FDA Talk Paper T00-14 (8), which indicated that as of December 31, 1999, use of cisapride was associated with 341 reports of arrhythmias and 80 reports of death, prompted its complete withdrawal from the US market in July 2000.

Perhaps the vigilant reader would have noted that the withdrawal of cisapride in the US was not entirely evidence-based. A recent study conducted in children on peritoneal dialysis found mild but significant increases in QTc intervals, which were mostly attributed to concomitant medications rather than cisapride *per se* (9). Whether cisapride is safe in the adult dialysis population remains largely unknown. In this issue of the Hong Kong Journal of Nephrology, Tse et al (10) addressed this issue by retrospectively comparing the clinical outcome of 85 chronic dialysis patients who had received cisapride versus that of 279 patients who had never taken cisapride. The authors found that the use of cisapride, regardless of dosage, does not increase mortality. Nevertheless, hypoalbuminemia and hypokalemia were identified as independent predictors of mortality in patients who had taken cisapride. Ironically, hypoalbuminemia could well be the very reason for prescribing a prokinetic agent for these patients in the first place. Hence, the clinician must exercise his own acumen by taking the appropriate precautionary measures which, as Tse et al have also partly pointed out, include (a) cautious reappraisal of the indication of cisapride; (b) detection of unrecognized underlying cardiac disease or QT interval prolongation; (c) correction of any pro-arrhythmic electrolyte disturbances before prescription; (d) judicious review of concomitant medications that may interact with cisapride; (e) serial monitoring of the QT interval and serum potassium level after commencing treatment; and (f) constant evaluation of the indication of continuing the prescription.

Where are the potential pitfalls in pharmacologic interaction? In general, cisapride must not be co-administered with agents that possess either of the following two major pharmacokinetic/pharmacodynamic properties: (a) inhibitors of cytochrome P450-3A4 enzymes (CYP-3A4) such as macrolides (11), new

antidepressants particularly nefazodone and fluvoxamine (12),azole antimycotics, diltiazem, cimetidine, and isoniazid. The rationale is that CYP-3A4 is the primary mode of cisapride metabolism. As such, attention must also be drawn to the recent identification of epoxybergamottin as a CYP-3A4 inhibitor in grapefruit (13); and (b) drugs with arrhythmogenic potential that prolong the QT interval, such as class Ia/III (by Vaughan Williams classification) antiarrhythmic drugs particularly sotalol (14), and the second-generation non-sedative selective H₁-receptor antihistamines such as loratadine, terfenadine, astemizole (15). The rationale is that these drugs share the same arrhythmogenic mechanism with cisapride in QT prolongation by specific, high affinity blockade of the cardiac K⁺ channel encoded by the human ether-a-go-go-related gene (HERG) in chromosome 7 (16).

What is the current status in Hong Kong? Following the withdrawal of cisapride in the US, a "PrepulsidTM

(Cisapride) Limited Access Programme" was implemented in June 2001 to prevent potentially fatal events related to cisapride usage. The mandatory Programme Form that includes a thorough checklist of contraindications must be signed by the physician, preferably a gastroenterologist, and the patient in quadruplicate to be retained by the institution/clinic in the patient's medical record, the pharmacy, the drug supplier, and the patient. It is not surprising that after the enforcement of such stringent procedures, cisapride has become almost an extinct item in this locality. Alternative prokinetic agents that the nephrologist may consider include domperidone, metoclopramide, and erythromycin. The ideal prokinetic agent—one that restores gastric motility without compromising cardiac HERG channels and does not depend on CYP-3A4 elimination—has yet to be formulated.

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